Xeljanz®

(Tofacitinib)

PRESCRIBER BROCHURE

PRESCRIBER BROCHURE

The contents of the Prescriber Brochure will be based on the final approved Summary of Product Characteristics (SPC).

This Prescriber Brochure intends to provide guidance on tofacitinib to the prescribing physicians with respect to therapeutic indications, dosing and administration including considerations for administration, instruction on monitoring laboratory parameters, precautions and warnings, patient counseling, reporting of adverse events, and a summary of the risk management plan.

XELJANZ® Prescriber Brochure

A guide to dosing, administration, monitoring, and risk management

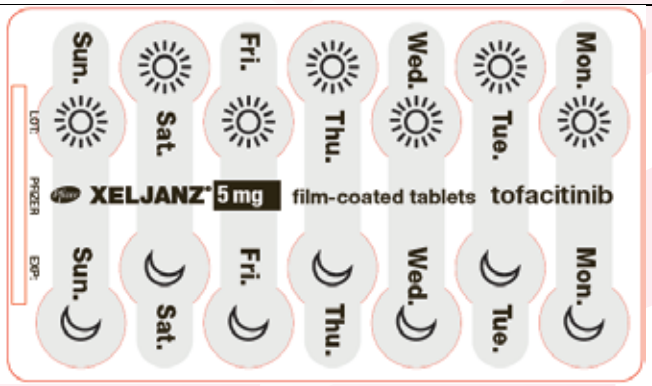
Therapeutic indications

• XELJANZ, an inhibitor of Janus kinases (JAKs), is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

• XELJANZ should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine

Posology and method of administration

XELJANZ treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Oral dosing	XELJANZ is available in 5 mg tablets
XELJANZ 5 mg BID	
Recommended dose is 5 mg administered twice daily	

XELJANZ should be avoided in combination with biological DMARDs and potent immunosuppressants because of the possibility of increased immunosuppression and increased risk of infection.

Considerations for administration

Contraindications

- None.

Prior to administering XELJANZ

- Discuss the risks with patients using **patient safety card** and **XELJANZ treatment initiation checklist** (see enclosed checklist for more details).
- Consider the risk and benefits of XELJANZ treatment carefully in patients who are at higher risk of developing serious infections including patients:
    - with chronic or recurrent infections,
    - who have been exposed to tuberculosis,
    - with a history of a serious or an opportunistic infection,
    - who have resided or travelled in areas of endemic tuberculosis or endemic mycoses,
    - who have underlying conditions that may predispose them to infection, such as diabetes mellitus.
- Evaluate and test the patient for latent or active TB infection. Patients with latent TB should be treated with standard antimycobacterial therapy before administering XELJANZ.
- All patients should be brought up to date with all immunisations in agreement with current immunisation guidelines.
- Screening for viral hepatitis should be performed in accordance with clinical guidelines.
- Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy
- Check patients' laboratory parameters including lymphocytes, neutrophils, and haemoglobin. Initiating treatment is not recommended in patients with:

- Low lymphocyte count (<500 cells/mm^3)
- Low absolute neutrophil count (<1000 cells/mm^3)
- Low haemoglobin (<9 g/dL)

Patients treated with XELJANZ should be given a patient safety card. An adequate supply will be provided to prescribers for distribution to patients (through Pfizer local country office distribution channels). **Patient should be advised to keep this card with them for at least 2 months after taking the last dose of XELJANZ** .

Monitoring of laboratory parameters:

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
Lymphocytes	At baseline, then every 3 months	Greater than or equal to 500 cells/mm^3	Maintain dose
		Less than 500 cells/mm^3 (confirmed by repeat testing))	Discontinue treatment
Neutrophils	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	ANC greater than 1000 cells/mm^3	Maintain dose
		ANC 500–1000 cells/mm^3	For persistent decreases in this range, interrupt tofacitinib dosing until ANC is greater than 1000 cells/mm^3. When ANC is greater than 1000, cells/mm^3 resume tofacitinib 5 mg twice daily.
		ANC less than 500 cells/mm^3	Discontinue treatment
Haemoglobin	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Maintain dose
		Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Interrupt the administration of tofacitinib until haemoglobin values have normalized
Lipids	After 8 weeks following initiation of tofacitinib therapy	NA	Managed according to clinical guidelines for the management of hyperlipidaemia

ANC=absolute neutrophil counts; NA=not applicable

Special warnings and precautions for use

Serious infections

The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were

reported with XELJANZ. Some patients have presented with disseminated rather than localised disease, and rheumatoid arthritis patients were often taking concomitant immunomodulating agents such as MTX or corticosteroids which, in addition to rheumatoid arthritis, may predispose them to infections. Other serious infections that were not reported in clinical studies may also occur (e.g., histoplasmosis and coccidioidomycosis).

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. Treatment should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Caution is recommended when tofacitinib treatment is used in the following patients:

- Elderly and diabetic patients given there is a higher incidence of infections in general
- Patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with XELJANZ in clinical trials and in the post-marketing setting although the role of JAK inhibition in these events is not known.
- Patients with lymphopenia

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ.

Viral reactivation

Viral reactivation has been reported with DMARD treatment and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. The risk of herpes zoster appears to be higher in Japanese patients treated with XELJANZ.

Malignancies and lymphoproliferative disorder [Excluding Non-melanoma Skin Cancer (NMSC)]

The possibility exists for XELJANZ to affect host defenses against malignancies. The impact of treatment with tofacitinib on the development and course of malignancies is not known, but malignancies were observed in clinical studies with tofacitinib.

Lymphomas have been observed in patients treated with XELJANZ. Patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk than the general population (up to several-fold) for the development of lymphoma, the role of XELJANZ, a Janus-kinase inhibitor, in the development of lymphoma is uncertain.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical trials although the role of Janus- kinase inhibition in these events is not known. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis.
Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Vaccination

- No data are available on the secondary transmission of infection by live vaccines to patients receiving XELJANZ.
- It is recommended that live vaccines not be given concurrently with tofacitinib.
- It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating XELJANZ therapy.
- The interval between live vaccinations and initiation of XELJANZ therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents. Consistent with these guidelines, if live zoster vaccine is administered, it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. Vaccination should occur at least 2 weeks but preferably 4 weeks before initiating immunomodulatory agents such as XELJANZ.

Use in Special Populations

Patients with renal impairment

- No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).
- XELJANZ dose should be reduced to 5 mg once daily in patients with severe renal impairment (creatinine clearance <30 mL/min).

Patients with hepatic impairment

- No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).
- XELJANZ dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment (Child Pugh B).

- Treatment with XELJANZ should not be used in patients with severe hepatic impairment (Child Pugh C).

Pediatric patients

The safety and efficacy of XELJANZ in children and adolescents less than 18 years of age have not yet been established.

Pregnancy and lactation

- XELJANZ should not be used during pregnancy unless clearly necessary.
- Women should not breast-feed while being treated with XELJANZ.

Women of childbearing potential

- Women of childbearing potential should be advised to use effective contraception during treatment with XELJANZ and for at least 4 weeks after the last dose.

FOR MORE DETAILS ON PRESCRIBING XELJANZ, PLEASE REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS.

Patient Counseling

It is important for you to discuss the risks associated with use of tofacitinib with your patients, and in applicable instances, with their caregivers.

A patient safety card has been developed to help patients understand the risks associated with XELJANZ, and remind them to seek immediate medical attention if they experience any listed signs and symptoms.

It is important for physicians to:

- provide the patient safety card to each patient who is prescribed with tofacitinib.
- remind patients to use the patient safety card.
- discuss the risks with each patient and ensure patient understanding of the treatment potential risks.
- ensure patients to carry the patient safety card with them, particularly when they visit doctors' office and/or the emergency room.

You should remind patients to seek immediate medical attention if they experience any of the following signs and symptoms.

- Experience possible symptoms of allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue or throat, itching or skin rash when taking tofacitinib, or soon after taking tofacitinib.

- Develop symptoms of an infection, such as fever, persistent cough, weight loss, or excessive tiredness.
- Have been in close contact with a person with TB.
- Develop abdominal signs and symptoms such as stomach pain, abdominal pain, blood in stool, or any change in bowel habits with fever.
- Develop yellow skin, nausea or vomiting.
- Are due to receive any vaccine. Patients should not receive certain types of vaccines while taking tofacitinib.
- Become pregnant or plan on becoming pregnant.

Reporting of Adverse Events

Please report any adverse events through the following channels
1. The National Pharmacovigilance & Drug Safety Centre (NPC)
Fax: +966 112057662 / Unified: 1999 / Toll free phone: 8002490000
E-mail: npc.drug@sfda.gov.sa Website: www.sfda.gov.sa/npc
Or
2. The Pharmacovigilance Department in Pfizer:
Email: SAU.AEReporting@Pfizer.com Tel.: 012 22 93 633

Risk Management Plan (RMP)

A risk management system, described in the risk management plan (RMP), is a set of pharmacovigilance activities and interventions required by the Saudi Food and Drug Authority (SFDA) to ensure that the benefits of the medicinal product outweigh its risks.

The XELJANZ RMP is developed:

- to identify, characterise, prevent or minimize risks relating to XELJANZ including the assessment of the effectiveness of those activities and interventions.

Risk Communication

In order to communicate certain risks about tofacitinib, Pfizer has worked with the SFDA to develop a detailed communication plan to communicate the risks described in the summary of product characteristics, including the following items:

- patient safety card
- prescriber brochure
- prescriber treatment initiation checklist
- prescriber treatment maintenance checklist

Two treatment checklists: initiation checklist and maintenance checklists, are developed for you to be used prior to and during tofacitinib treatment. They intend to remind you of the risks associated with use of tofacitinib and the recommended tests before and during the tofacitinib treatment.